67 83. The method according to claim 64, wherein the duration is three months.

69 73 84. A method for distributing an active agent over a mammal's body and/or in the sebaceous glands of said mammal and thereby control fleas and ticks for a long period of time which comprises applying to the skin of said mammal a synergistic composition according to claim 5.

68 72 85. The method according to claim 67, wherein the synergistic combination comprises synergistic effective amounts of Fipronil and methoprene.--

REMARKS

The invention provides compositions comprising 1-N-arylpyrazoles and insect growth regulators which exhibit synergistic activity against fleas and ticks when said compositions are applied topically to the skin of a mammal. Applicants discovered that the inventive compositions are ovicidally active for a longer duration of time than one would expect based upon the activity of the individual active agents. This invention further provides for a method of controlling flea and tick infestations by distributing the active agent over the mammal's body through the sebaceous glands.

Pursuant to 37 CFR 1.136(a) Applicants petition the Assistant Commissioner to extend the time period for Applicants to respond to the outstanding Office Action by three (3) months; i.e., up to and including September 24, 1999. A check for $870.00 is enclosed to cover the cost of this petition. If further fees are due, the Assistant Commissioner is authorized to charge such fees, or credit any overpayment, to Deposit Account 50-0320.

Claims 1 to 37, 49 to 58 and 60 to 85 are pending in this application. This Amendment cancels claims 31 to 48 and 59, without prejudice and adds claims 60 to 84.

Support for the terms "synergistic" and "synergistic effective amount" now recited in the claims is found on page 1, line 5 of the specification. Claims 64 to 82 find support in original claims 38 to 40 and 59 and in the specification on page 17, line 30 (for two months). Support for claims 83 and 84 is found in the paragraph bridging page 17 and 18. Thus, no new matter is added by this Amendment.

The withdrawal of the rejection of claims 1 to 48 under 35 U.S.C. §§ 101 and 112, second paragraph and on the grounds of provisional double patenting is greatly appreciated.

The common name for 1-[2,6-$Cl_2$4-CF_3-phenyl] 3-CN 4-[SO-CF_3]5-NH_2 pyrazole, Fipronil, has been inserted into claims 8, 9 and 31.

Claims 1 to 48 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Duffy et al., U.S. Patent No. 5,612,047, ("Duffy") Postal et al. ("Postal") and Skillman et al., PCT 95/33380 ("Skillman"). In view of the Declaration of Dr. Marchiondo and for the reasons provided below, Applicants urge that the present compositions are patentable over the prior publications as none of these publications teaches or suggests that synergistic ovocidal activity is obtained when a 1-N-arylpyrazole derivative is combined with an insect growth regulator. Moreover, none of this publication suggests a method where the active agents difference through the sebaceous glands.

Duffy is said to "teach microemulsion formulations for the control of ticks and fleas comprising IGRs including juvenile hormones, juvenoids and chitin synthesis inhibitors (e.g., methoprene, col. 2, lines 32-37), in addition to active agents such as pyriproxyfen (line 53). The compositions may be used as "dips, sprays, pour-ons, spot-ons, conditioning creams, aerosol mouses, etc. "(col. 5, lines 20-27). Postal is said to teach the Fripronil is known as a spray formulation for controlling fleas in dogs and cats. *Id.* Skillman is cited "to show that each of the

active agents...was known in the art." *Id.* From this the rejection concludes that it would have been *prima facie* obvious to combine the "two compositions, each of which is taught in the prior art to be useful for the same purpose in order to form a third composition to be useful for the very same purpose." Office Action at 4. Applicants respectfully disagree with this position because none of these references taken alone or in any fair combination suggest that one observes synergistic ovicidal activity when a fipronil derivative is combined with an insect growth regulator.

Contrary to the position taken in the rejection none of the prior patents suggests that one may obtain long-lasting protection against fleas and ticks by topically applying the inventive compositions on the skin of the animals. Moreover, none of these references suggests that one can combat flea and ticks by distributing the active agents over the mammal's body through the sebaceous gland.

As discussed above, Duffy only discloses the use of microemulsions containing IGRs as dips, sprays, pour-on or spot-on compositions. The patent does not disclose N-arylpyrazole derivatives. The rejection relies upon Postal to teach that fipronil is known to control fleas and ticks. However, Postal discloses spray formulations. As spray formulations are totally different from the inventive formulation, which are applied topically and diffuse throughout the body by the sebaceous glands. Postal does not suggest the present claims, especially claims 83 and 84.

Moreover, the literature cited in the rejection does not suggest that one can obtain synergistic results when the inventive formulations are used treat ticks and fleas in mammals. In support of this position Applicants present the Declaration of Dr. Marchiondo.

The Declaration presents *in vitro* and *in vivo* data. From the data, Dr. Marchiondo, an expert in his field, concludes that the inventive compositions possess synergistic activity. Moreover, Dr. Marchiondo concludes that, in view of similar activities other, compounds which mimic the juvenile hormone would also be expected to possess synergistic activity.

Moreover, in view of the literature, one would be able to extrapolate the data to include other fipronil-type compounds.

Phenylpyrazoles are a class of insecticides which possess excellent insecticidal activity against insect pests including blood-sucking pests such as ticks, and fleas etc., which are parasites on animals. Phenylpyrazoles are within the class of compounds known as arylheterocycles. This class of agents kills insects by acting on the gamma-butyric acid (GABA) receptor of invertebrates (*See, e.g.,* Bloomquist, Ann Rev Entomol, 41:163-90 (1996) (Abstract attached).

The specification at page 5 further teaches that compounds according to formula (I) are "very lipophilic and of high vapor pressure (low volatility)". Thus, the compounds have a very high affinity for the sebum and are taken up by the sebaceous glands. Indeed, Cochet et al., Eur J Drug Metab Pharmacokinet 22(3):211-6 (1997) (copy of Abstract attached) showed that fipronil, an exemplary compound within formula (I), indeed is taken up in the sebaceous glands (and epithelial layers) of animals. Since the compounds of formula (I) are "very lipophilic and of high vapor pressure (low volatility)" there is no reason to doubt that they too, like fipronil, will be taken up in the sebaceous glands (and epithelial layers) of animals.

Hainzl et al., PNAS USA 93(23):1276407 (1996) (copy of Abstract attached) showed that desulfinylfipronil, the trifluoromethylpyrazole derivative of fipronil, is formed when

fipronil is used as a plant insecticide (exposed to sunlight). Hainzl et al. 1996 also showed that desulfinylfipronil, the trifluoromethylpyrazole derivative of fipronil, a phenylpyrazole related to fipronil, has high neuroactivity, like fipronil and suggests that desulfinylfipronil can be a significant contributor to the effectiveness of fipronil as an insecticide for crop protection.

Since fipronil derivatives have neurotoxicity, there is no reason to doubt that compounds of formula (I) will likewise be active against fleas and ticks. Hainzl et al. 1996 states that the trifluoromethylsulfinyl moiety of fipronil is "presumably important in its outstanding performance." In this regard, note that in formula (I) compounds, it is preferred that R_2 be $S(O)_nR_3$ with R_3 being preferably alkyl or haloalkyl (application at page 7), with particular mention being made of formula (I) compounds wherein n=0 and R_3 is CF_3, and formula (I) compounds wherein n=1 and R_3 is ethyl (application at page 9). Further page 9 teaches a preferred class of compounds of formula (I) consists of those wherein R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, is a halogen atom, and/or R_{13} is haloalkyl.

Thus the skilled artisan, looking to the specification, is directed to compounds of formula (I) having the trifluoromethylsulfinyl moiety of fipronil which is recognized as "important in its outstanding performance", as well as to formula (I) compounds wherein n=0 and R_3 is CF_3 or wherein n=1 and R_3 is ethyl (and thus R_2 is $S(O)_nR_3$), and compounds of formula (I) wherein R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, is a halogen atom, and R_{13} is haloalkyl (and thus R_2 is $S(O)_nR_3$), such that the specification provides a great deal of guidance, in addition to the Examples as to compounds within formula (I) that are especially useful in the practice of the invention; and, the skilled artisan would likely initially select those preferred compounds in any screening.

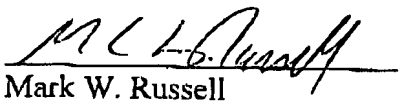
Further still, Hainzl et al. 1996 was followed by Hainzl et al., Chem Res Toxicol 11(12):1529-35 (1998) (copy of Abstract attached), wherein the authors showed that phenylpyrazoles related to fipronil, such as desulfinyl fipronil and fipronil sulfone, indeed acted on the GABA receptor of insects. Thus those compounds too will act as insecticides, like fipronil.

Accordingly, it is clear that compounds in addition to fipronil, within formula (I), act as insecticides. Likewise, the mechanism of action of IGRs is known in the art. Accordingly, one skilled in the art would expect that the data presented in the Declaration could be extrapolated to include all of the combinations recited in claim 1.

Therefore, in view of the foregoing, reconsideration and withdrawal of this rejection is respectfully requested.

Favorable action is earnestly solicited.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 
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Annu Rev Entomol 1996;41:163-90

Ion channels as targets for insecticides.

Bloomquist JR

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Ion channels are the primary target sites for several classes of natural and synthetic insecticidal compounds. The voltage-sensitive sodium channel is the major target site for DDT and pyrethroids, the veratrum alkaloids, and N-alkylamides. Recently, neurotoxic proteins from arthropod venoms, some of which specifically attack insect sodium channels, have been engineered into baculoviruses to act as biopesticides. The synthetic pyrazolines also primarily affect the sodium channel, although some members of this group target neuronal calcium channels as well. The ryanoids have also found use as insecticides, and these materials induce muscle contracture by irreversible activation of the calcium-release channel of the sarcoplasmic reticulum. The arylheterocycles (e.g. endosulfan and fipronil) are potent convulsants and insecticides that block the GABA-gated chloride channel. In contrast, the avermectins activate both ligand- and voltage-gated chloride channels, which leads to paralysis. At field-use rates, a neurotoxic effect of the ecdysteroid agonist RH-5849 is observed that involves blockage of both muscle and neuronal potassium channels. The future use of ion channels as targets for chemical and genetically engineered insecticides is also discussed.

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- Review, academic

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Eur J Drug Metab Pharmacokinet 1997 Jul-Sep;22(3):211-6

Skin distribution of fipronil by microautoradiography following topical administration to the beagle dog.

Cochet P, Birckel P, Bromet-Petit M, Bromet N, Weil A

Biotec Centre, Orleans, France.

To investigate the localisation of fipronil in dog skin, [14C]-fipronil was topically applied to a male beagle dog (spot-on administration) at the therapeutic dose of 10 mg/kg. By means of autohistoradiography, the radioactivity was precisely detected in the skin and appendages at various intervals after application. Radioactivity was predominantly observed within the stratum corneum, the viable epidermis, and in the pilo-sebaceous units (mainly in the sebaceous glands and epithelial layers). [14C]-fipronil was significantly detected in these structures up to 56 days post-treatment, in the application zone (neck) but also in the lumbar zone, thus indicating the mechanical displacement of fipronil. No radioactivity was detected in either the dermal or the hypodermal layers, confirming the low percutaneous passage of fipronil.

PMID: 9358201, UI: 98023038

Proc Natl Acad Sci U S A 1996 Nov 12;93(23):12764-7

Fipronil insecticide: novel photochemical desulfinylation with retention of neurotoxicity.

Hainzl D, Casida JE

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Fipronil is an outstanding new insecticide for crop protection with good selectivity between insects and mammals. The insecticidal action involves blocking the lambda-aminobutyric acid-gated chloride channel with much greater sensitivity of this target in insects than in mammals. Fipronil contains a trifluoromethylsulfinyl moiety that is unique among the agrochemicals and therefore presumably important in its outstanding performance. We find that this substituent unexpectedly undergoes a novel and facile photoextrusion reaction on plants upon exposure to sunlight, yielding the corresponding trifluoromethylpyrazole, i.e., the desulfinyl derivative. The persistence of this photoproduct and its high neuroactivity, resulting from blocking the lambda-aminobutyric acid-gated chloride channel, suggest that it may be a significant contributor to the effectiveness of fipronil. In addition, desulfinylfipronil is not a metabolite in mammals, so the safety evaluations must take into account not only the parent compound but also this completely new environmental product.

PMID: 8917493, UI: 97075066

Chem Res Toxicol 1998 Dec;11(12):1529-35

Mechanisms for selective toxicity of fipronil insecticide and its sulfone metabolite and desulfinyl photoproduct.

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Fipronil, an N-phenylpyrazole with a trifluoromethylsulfinyl substituent, initiated the second generation of insecticides acting at the gamma-aminobutyric acid (GABA) receptor to block the chloride channel. The first generation includes the polychlorocycloalkanes alpha-endosulfan and lindane. In this study, we examine the mechanisms for selective toxicity of the sulfoxide fipronil and its sulfone metabolite and desulfinyl photoproduct relative to their target site interactions in vitro and ex vivo and the importance in fipronil action of biooxidation to the sulfone. Differences in GABA receptor sensitivity, assayed by displacement of 4'-ethynyl-4-n-[2, 3-3H2]propylbicycloorthobenzoate ([3H]EBOB) from the noncompetitive blocker site, appear to be a major factor in fipronil being much more toxic to the insects (housefly and fruit fly) than to the vertebrates (humans, dogs, mice, chickens, quail, and salmon) examined; in insects, the IC50s range from 3 to 12 nM for fipronil and its sulfone and desulfinyl derivatives, while in vertebrates, the IC50 average values are 1103, 175, and 129 nM for fipronil, fipronil sulfone, and desulfinyl fipronil, respectively. The insect relative to the vertebrate specificity decreases in the following order: fipronil > lindane > desulfinyl fipronil > fipronil sulfone > alpha-endosulfan. Ex vivo inhibition of [3H]EBOB binding in mouse brain is similar for fipronil and its sulfone and desulfinyl derivatives at the LD50 dose, but surprisingly, at higher doses fipronil can be lethal without detectably blocking the [3H]EBOB site. The P450 inhibitor piperonyl butoxide, acting in houseflies, increases the metabolic stability and effectiveness of fipronil and the sulfone but not those of the desulfinyl compound, and in mice it completely blocks the sulfoxide to sulfone conversion without altering the poisoning. Thus, the selective toxicity of fipronil and fipronil-derived residues is due in part to the higher potency of the parent compound at the insect versus the mammalian GABA receptor but is also dependent on the relative rates of conversion to the more persistent and less selective sulfone metabolite and desulfinyl photoproduct.

PMID: 9860498, UI: 99077671